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COMBINATION THERAPY

Abstract:

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The present invention relates to a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human which is optionally being treated with ionising radiation, particularly a method for the treatment of a cancer, particularly a cancer involving a solid tumour, which comprises the administration of AZD2171 in combination with gemcitabine; to a pharmaceutical composition comprising AZD2171 and gemcitabine; to a combination product comprising AZD2171 and gemcitabine for use in a method of treatment of a human or animal body by therapy; to a kit comprising AZD2171 and gemcitabine; to the use of AZD2171 and gemcitabine in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human which is optionally being treated with ionising radiation. Data supplied from the esp@cenet database - Worldwide

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(54) Title: COMBINATION THERAPY

(57) Abstract: The present invention relates to a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human which is optionally being treated with ionising radiation, particularly a method for the treatment of a cancer, particularly a cancer involving a solid tumour, which comprises the administration of AZD2171 in combination with gemcitabine; to a pharmaceutical composition comprising AZD2171 and gemcitabine; to a combination product comprising AZD2171 and gemcitabine for use in a method of treatment of a human or animal body by therapy; to a kit comprising AZD2171 and gemcitabine; to the use of AZD2171 and gemcitabine in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human which is optionally being treated with ionising radiation.



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COMBINATION THERAPY

The present invention relates to a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human which is optionally being treated with ionising radiation, particularly a method for the treatment of a cancer, particularly a cancer involving a solid tumour, which comprises the administration of AZD2171 in combination with gemcitabine; to a pharmaceutical composition comprising AZD2171 and gemcitabine; to a combination product comprising AZD2171 and gemcitabine for use in a method of treatment of a human or animal body by therapy; to a kit comprising AZD2171 and gemcitabine; to the use of AZD2171 and gemcitabine in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human which is optionally being treated with ionising radiation.

Normal angiogenesis plays an important role in a variety of processes including embryonic development, wound healing and several components of female reproductive function. Undesirable or pathological angiogenesis has been associated with disease states including diabetic retinopathy, psoriasis, cancer, rheumatoid arthritis, atheroma, Kaposi's sarcoma and haemangioma (Fan et al, 1995, Trends Pharmacol. Sci. 16: 57-66; Folkman, 1995, Nature Medicine 1: 27-31). Alteration of vascular permeability is thought to play a role in both normal and pathological physiological processes (Cullinan-Bove et al, 1993, Endocrinology 133: 829-837; Senger et al, 1993, Cancer and Metastasis Reviews, 12: 303-324). Several polypeptides with *in vitro* endothelial cell growth promoting activity have been identified including, acidic and basic fibroblast growth factors (aFGF & bFGF) and vascular endothelial growth factor (VEGF). By virtue of the restricted expression of its receptors, the growth factor activity of VEGF, in contrast to that of the FGFs, is relatively specific towards endothelial cells. Recent evidence indicates that VEGF is an important stimulator of both normal and pathological angiogenesis (Jakeman et al, 1993, Endocrinology, 133: 848-859; Kolch et al, 1995, Breast Cancer Research and Treatment, 36:139-155) and vascular permeability (Connolly et al, 1989, J. Biol. Chem. 264: 20017-20024). Antagonism of VEGF action by sequestration of VEGF with antibody can result in inhibition of tumour growth (Kim et al, 1993, Nature 362: 841-844).

Receptor tyrosine kinases (RTKs) are important in the transmission of biochemical signals across the plasma membrane of cells. These transmembrane molecules

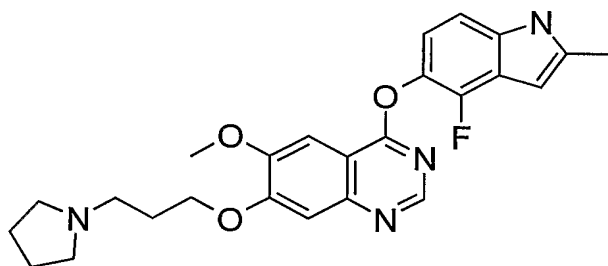
characteristically consist of an extracellular ligand-binding domain connected through a segment in the plasma membrane to an intracellular tyrosine kinase domain. Binding of ligand to the receptor results in stimulation of the receptor-associated tyrosine kinase activity which leads to phosphorylation of tyrosine residues on both the receptor and other intracellular molecules. These changes in tyrosine phosphorylation initiate a signalling cascade leading to a variety of cellular responses. To date, at least nineteen distinct RTK subfamilies, defined by amino acid sequence homology, have been identified. One of these subfamilies is presently comprised by the *fms*-like tyrosine kinase receptor, Flt-1 (also referred to as VEGFR-1), the kinase insert domain-containing receptor, KDR (also referred to as VEGFR-2 or Flk-1), and another *fms*-like tyrosine kinase receptor, Flt-4. Two of these related RTKs, Flt-1 and KDR, have been shown to bind VEGF with high affinity (De Vries et al, 1992, *Science* 255: 989-991; Terman et al, 1992, *Biochem. Biophys. Res. Comm.* 1992, 187: 1579-1586). Binding of VEGF to these receptors expressed in heterologous cells has been associated with changes in the tyrosine phosphorylation status of cellular proteins and calcium fluxes.

VEGF is a key stimulus for vasculogenesis and angiogenesis. This cytokine induces a vascular sprouting phenotype by inducing endothelial cell proliferation, protease expression and migration, and subsequent organisation of cells to form a capillary tube (Keck, P.J., Hauser, S.D., Krivi, G., Sanzo, K., Warren, T., Feder, J., and Connolly, D.T., *Science* (Washington DC), 246: 1309-1312, 1989; Lamoreaux, W.J., Fitzgerald, M.E., Reiner, A., Hasty, K.A., and Charles, S.T., *Microvasc. Res.*, 55: 29-42, 1998; Pepper, M.S., Montesano, R., Mandroita, S.J., Orci, L. and Vassalli, J.D., *Enzyme Protein*, 49: 138-162, 1996.). In addition, VEGF induces significant vascular permeability (Dvorak, H.F., Detmar, M., Claffey, K.P., Nagy, J.A., van de Water, L., and Senger, D.R., *Int. Arch. Allergy Immunol.*, 107: 233-235, 1995; Bates, D.O., Heald, R.I., Curry, F.E. and Williams, B. J. *Physiol. (Lond.)*, 533: 263-272, 2001), promoting formation of a hyper-permeable, immature vascular network which is characteristic of pathological angiogenesis.

It has been shown that activation of KDR alone is sufficient to promote all of the major phenotypic responses to VEGF, including endothelial cell proliferation, migration, and survival, and the induction of vascular permeability (Meyer, M., Clauss, M., Lepplé-Wienhues, A., Waltenberger, J., Augustin, H.G., Ziche, M., Lanz, C., Büttner, M., Rziha, H.-J., and Dehio, C., *EMBO J.*, 18: 363-374, 1999; Zeng, H., Sanyal, S. and Mukhopadhyay,

D., J. Biol. Chem., 276: 32714-32719, 2001; Gille, H., Kowalski, J., Li, B., LeCouter, J., Moffat, B, Zioncheck, T.F., Pelletier, N. and Ferrara, N., J. Biol. Chem., 276: 3222-3230, 2001).

Quinazoline derivatives which are inhibitors of VEGF receptor tyrosine kinase are described in International Patent Application Publication No. WO 00/47212. AZD2171 is described in WO 00/47212 and is Example 240 therein. AZD2171 is 4-(4-fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline:



AZD2171

AZD2171 shows excellent activity in the *in vitro* (a) enzyme and (b) HUVEC assays that are described in WO 00/47212 (pages 80-83). The AZD2171 IC₅₀ values for inhibition of isolated KDR (VEGFR-2) and Flt-1 (VEGFR-1) tyrosine kinase activities in the enzyme assay were <2 nM and 5 ± 2 nM respectively. AZD2171 inhibits VEGF-stimulated endothelial cell proliferation potently (IC₅₀ value of 0.4 ± 0.2 nM in the HUVEC assay), but does not inhibit basal endothelial cell proliferation appreciably at a > 1250 fold greater concentration (IC₅₀ value is > 500 nM). The growth of a Calu-6 tumour xenograft in the *in vivo* solid tumour model described in WO 00/47212 (page 83) was inhibited by 49% **, 69% *** and 91% *** following 28 days of once-daily oral treatment with 1.5, 3 and 6 mg/kg/day AZD2171 respectively (P** < 0.01, P*** < 0.0001; one-tailed t test). AZD2171 has been shown to elicit broad-spectrum anti-tumour activity in a range of models following once-daily oral administration, (Wedge et al., 2005, Cancer Research 65: 4389-4440).

In WO 00/47212 it is stated that compounds of the invention: “may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or treatments. Such conjoint treatment may be

achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment.”

WO 00/47212 then goes on to describe examples of such conjoint treatment including surgery, radiotherapy and various types of chemotherapeutic agent.

5 Nowhere in WO 00/47212 does it suggest the combination of a compound of the invention and gemcitabine for the treatment of any disease state including cancer.

Nowhere in WO 00/47212 is the specific combination of AZD2171 and gemcitabine suggested.

10 Nowhere in WO 00/47212 does it state that use of any compound of the invention therein with other treatments will produce surprisingly beneficial effects.

A triple combination of a VEGF RTK inhibitor (PTK 787), an EGF RTK inhibitor (PKI 166) and gemcitabine is described in Baker et al, Cancer Research 62, 1996 2003, April 1, 2002. The authors concluded that a combination of either PTK 787 with gemcitabine or PKI 166 with gemcitabine was beneficial but that the triple combination
15 did not produce additive therapeutic effects.

A combination of gemcitabine with DC101, a VEGF receptor-2 antibody (anti-KDR antibody) is described in Bruns et al, International Journal of Cancer vol 102, issue 2, 2002 pages 101-108.

20 Unexpectedly and surprisingly we have now found that the particular compound AZD2171 used in combination with a particular selection from the combination therapies listed in WO 00/47212, namely with gemcitabine, produces significantly better effects than any one of AZD2171 and gemcitabine used alone. In particular, AZD2171 used in combination with gemcitabine produces significantly better effects on solid tumours than any one of AZD2171 and gemcitabine used alone.

25 Gemcitabine is (INN) 2'-deoxy-2',2'-difluorocytidine monohydrochloride (β -isomer).

Gemcitabine is also known as Gemzar TM (Trademark of Lilly) and it is a cytotoxic agent. It is an anti-metabolite which causes inhibition of DNA synthesis.

30 Anti-cancer effects of a method of treatment of the present invention include, but are not limited to, anti-tumour effects, the response rate, the time to disease progression and the survival rate. Anti-tumour effects of a method of treatment of the present invention include but are not limited to, inhibition of tumour growth, tumour growth delay,

regression of tumour, shrinkage of tumour, increased time to regrowth of tumour on cessation of treatment, slowing of disease progression. It is expected that when a method of treatment of the present invention is administered to a warm-blooded animal such as a human, in need of treatment for cancer, said method of treatment will produce an effect, as measured by, for example, one or more of: the extent of the anti-tumour effect, the response rate, the time to disease progression and the survival rate. Anti-cancer effects include prophylactic treatment as well as treatment of existing disease.

According to the present invention there is provided a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of gemcitabine.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of gemcitabine.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer involving a solid tumour in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of gemcitabine.

According to a further aspect of the present invention there is provided a method for the treatment of cancer of the pancreas in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of gemcitabine.

According to a further aspect of the present invention there is provided a method for the treatment of non-small cell lung cancer (NSCLC) in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of gemcitabine.

According to a further aspect of the present invention there is provided a method for the treatment of breast cancer in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of gemcitabine.

According to a further aspect of the present invention there is provided a method for the treatment of cancer of the bladder in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of gemcitabine.

According to a further aspect of the present invention there is provided a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of gemcitabine; wherein AZD2171 and gemcitabine may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of gemcitabine; wherein AZD2171 and gemcitabine may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer involving a solid tumour in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of gemcitabine; wherein AZD2171 and gemcitabine may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a method for the treatment of cancer of the pancreas in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a

pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of gemcitabine; wherein AZD2171 and gemcitabine may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a method
5 for the treatment of non-small cell lung cancer (NSCLC) in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of gemcitabine; wherein AZD2171 and gemcitabine may each optionally be administered together with a pharmaceutically acceptable excipient or
10 carrier.

According to a further aspect of the present invention there is provided a method for the treatment of breast cancer in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective
15 amount of gemcitabine; wherein AZD2171 and gemcitabine may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a method for the treatment of bladder cancer in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a
20 pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of gemcitabine; wherein AZD2171 and gemcitabine may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises AZD2171 or a pharmaceutically acceptable salt thereof, and
25 gemcitabine in association with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a combination product comprising AZD2171 or a pharmaceutically acceptable salt thereof and gemcitabine, for use in a method of treatment of a human or animal body by therapy.

According to a further aspect of the present invention there is provided a kit
30 comprising AZD2171 or a pharmaceutically acceptable salt thereof, and gemcitabine.

According to a further aspect of the present invention there is provided a kit comprising:

- a) AZD2171 or a pharmaceutically acceptable salt thereof in a first unit dosage form;
- b) gemcitabine in a second unit dosage form; and
- c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit
5 comprising:

- a) AZD2171 or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable excipient or carrier, in a first unit dosage form;
- b) gemcitabine together with a pharmaceutically acceptable excipient or carrier, in a second unit dosage form; and
- 10 c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided the use of AZD2171 or a pharmaceutically acceptable salt thereof and gemcitabine in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human.

15 According to a further aspect of the present invention there is provided the use of AZD2171 or a pharmaceutically acceptable salt thereof and gemcitabine in the manufacture of a medicament for use in the production of an anti-cancer effect in a warm-blooded animal such as a human.

According to a further aspect of the present invention there is provided the use of
20 AZD2171 or a pharmaceutically acceptable salt thereof and gemcitabine in the manufacture of a medicament for use in the production of an anti-tumour effect in a warm-blooded animal such as a human.

According to a further aspect of the present invention there is provided the use of
25 AZD2171 or a pharmaceutically acceptable salt thereof and gemcitabine in the manufacture of a medicament for use in the production of an anti-tumour effect in a warm-blooded animal such as a human wherein the tumour is a tumour of the pancreas.

According to a further aspect of the present invention there is provided the use of
30 AZD2171 or a pharmaceutically acceptable salt thereof and gemcitabine in the manufacture of a medicament for use in the production of an anti-cancer effect in a warm-blooded animal such as a human wherein the cancer is non-small cell lung cancer (NSCLC).

According to a further aspect of the present invention there is provided the use of AZD2171 or a pharmaceutically acceptable salt thereof and gemcitabine in the manufacture of a medicament for use in the production of an anti-tumour effect in a warm-blooded animal such as a human wherein the tumour is a non-small cell tumour of the lung.

According to a further aspect of the present invention there is provided the use of AZD2171 or a pharmaceutically acceptable salt thereof and gemcitabine in the manufacture of a medicament for use in the production of an anti-cancer effect in a warm-blooded animal such as a human wherein the cancer is pancreatic cancer.

According to a further aspect of the present invention there is provided the use of AZD2171 or a pharmaceutically acceptable salt thereof and gemcitabine in the manufacture of a medicament for use in the production of an anti-tumour effect in a warm-blooded animal such as a human wherein the tumour is a tumour of the bladder.

According to a further aspect of the present invention there is provided the use of AZD2171 or a pharmaceutically acceptable salt thereof and gemcitabine in the manufacture of a medicament for use in the production of an anti-cancer effect in a warm-blooded animal such as a human wherein the cancer is bladder cancer.

According to a further aspect of the present invention there is provided the use of AZD2171 or a pharmaceutically acceptable salt thereof and gemcitabine in the manufacture of a medicament for use in the production of an anti-tumour effect in a warm-blooded animal such as a human wherein the tumour is a tumour of the breast.

According to a further aspect of the present invention there is provided the use of AZD2171 or a pharmaceutically acceptable salt thereof and gemcitabine in the manufacture of a medicament for use in the production of an anti-cancer effect in a warm-blooded animal such as a human wherein the cancer is breast cancer.

According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable excipient or carrier, and the simultaneous, sequential or separate administration of an effective amount of gemcitabine; wherein gemcitabine may optionally be administered together with a pharmaceutically acceptable excipient or carrier; to a warm-blooded animal such as a human in need of such therapeutic treatment.

Such therapeutic treatment includes an antiangiogenic and/or vascular permeability effect, an anti-cancer effect and an anti-tumour effect.

A combination treatment of the present invention as defined herein may be achieved by way of the simultaneous, sequential or separate administration of the individual components of said treatment. A combination treatment as defined herein may be applied as a sole therapy or may involve surgery or radiotherapy or an additional chemotherapeutic agent in addition to a combination treatment of the invention. Surgery may comprise the step of partial or complete tumour resection, prior to, during or after the administration of the combination treatment with AZD2171 described herein.

Other chemotherapeutic agents for optional use with a combination treatment of the present invention include those described in WO 00/47212 which is incorporated herein by reference. Such chemotherapy may cover five main categories of therapeutic agent:

- (i) other antiangiogenic agents including vascular targeting agents;
- (ii) cytostatic agents;
- (iii) biological response modifiers (for example interferon);
- (iv) antibodies (for example edrecolomab); and
- (v) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology; and other categories of agent are:
 - (vi) antisense therapies;
 - (vii) gene therapy approaches; and
 - (ix) immunotherapy approaches.

Particular examples of chemotherapeutic agents for use with a combination treatment of the present invention are raltitrexed, etoposide, vinorelbine, paclitaxel, docetaxel, cisplatin, oxaliplatin, carboplatin, irinotecan (CPT-11), 5-fluorouracil (5-FU, (including capecitabine)) and hydroxyurea. Such combinations are expected to be particularly useful for the treatment of cancer of the lung, head and neck, brain, colon, rectum, oesophagus, stomach, cervix, ovary, skin, breast, bladder, prostate, pancreas and including haematological malignancies. Such combinations are expected to be more particularly useful for the treatment of cancer of the pancreas, non-small cell lung cancer (NSCLC), breast cancer and bladder cancer.

The administration of a triple combination of AZD2171, gemcitabine and ionising radiation may produce effects, such as anti-tumour effects, greater than those achieved

with any of AZD2171, gemcitabine and ionising radiation used alone, greater than those achieved with the combination of AZD2171 and gemcitabine, greater than those achieved with the combination of AZD2171 and ionising radiation, greater than those achieved with the combination of gemcitabine and ionising radiation.

5 According to the present invention there is provided a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of gemcitabine and before, after or simultaneously with an
10 effective amount of ionising radiation.

 According to a further aspect of the present invention there is provided a method for the treatment of a cancer in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of
15 gemcitabine and before, after or simultaneously with an effective amount of ionising radiation.

 According to a further aspect of the present invention there is provided a method for the treatment of a cancer involving a solid tumour in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or
20 a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of gemcitabine and before, after or simultaneously with an effective amount of ionising radiation.

 According to a further aspect of the present invention there is provided a method for the treatment of cancer of the pancreas in a warm-blooded animal such as a human,
25 which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of gemcitabine and before, after or simultaneously with an effective amount of ionising radiation.

 According to a further aspect of the present invention there is provided a method
30 for the treatment of non-small cell lung cancer (NSCLC) in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously

with an effective amount of gemcitabine and before, after or simultaneously with an effective amount of ionising radiation.

According to a further aspect of the present invention there is provided a method for the treatment of breast cancer in a warm-blooded animal such as a human, which
5 comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of gemcitabine and before, after or simultaneously with an effective amount of ionising radiation.

According to a further aspect of the present invention there is provided a method
10 for the treatment of bladder cancer in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of gemcitabine and before, after or simultaneously with an effective amount of ionising radiation.

According to a further aspect of the present invention there is provided a method
15 for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of gemcitabine and before, after or
20 simultaneously with an effective amount of ionising radiation, wherein AZD2171 and gemcitabine may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer in a warm-blooded animal such as a human, which comprises
25 administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of gemcitabine and before, after or simultaneously with an effective amount of ionising radiation, wherein AZD2171 and gemcitabine may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a method
30 for the treatment of a cancer involving a solid tumour in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or

a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of gemcitabine and before, after or simultaneously with an effective amount of ionising radiation, wherein AZD2171 and gemcitabine may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

5 According to a further aspect of the present invention there is provided a method for the treatment of cancer of the pancreas in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of gemcitabine and before, after or simultaneously with an effective amount of
10 ionising radiation, wherein AZD2171 and gemcitabine may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

 According to a further aspect of the present invention there is provided a method for the treatment of non-small cell lung cancer (NSCLC) in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of
15 AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of gemcitabine and before, after or simultaneously with an effective amount of ionising radiation, wherein AZD2171 and gemcitabine may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

20 According to a further aspect of the present invention there is provided a method for the treatment of breast cancer in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of gemcitabine and before, after or simultaneously with an effective amount of
25 ionising radiation, wherein AZD2171 and gemcitabine may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

 According to a further aspect of the present invention there is provided a method for the treatment of bladder cancer in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a
30 pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of gemcitabine and before, after or simultaneously with an effective amount of

ionising radiation, wherein AZD2171 and gemcitabine may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided the use of AZD2171 or a pharmaceutically acceptable salt thereof and gemcitabine in the
5 manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human which is being treated with ionising radiation.

According to a further aspect of the present invention there is provided the use of AZD2171 or a pharmaceutically acceptable salt thereof and gemcitabine in the
10 manufacture of a medicament for use in the production of an anti-cancer effect in a warm-blooded animal such as a human which is being treated with ionising radiation.

According to a further aspect of the present invention there is provided the use of AZD2171 or a pharmaceutically acceptable salt thereof and gemcitabine in the
15 manufacture of a medicament for use in the production of an anti-tumour effect in a warm-blooded animal such as a human which is being treated with ionising radiation.

According to a further aspect of the present invention there is provided the use of AZD2171 or a pharmaceutically acceptable salt thereof and gemcitabine in the
manufacture of a medicament for use in the production of an anti-tumour effect in a
warm-blooded animal such as a human which is being treated with ionising radiation
20 wherein the tumour is a tumour of the pancreas.

According to a further aspect of the present invention there is provided the use of AZD2171 or a pharmaceutically acceptable salt thereof and gemcitabine in the
manufacture of a medicament for use in the production of an anti-cancer effect in a
warm-blooded animal such as a human which is being treated with ionising radiation
25 wherein the cancer is non-small cell lung cancer (NSCLC).

According to a further aspect of the present invention there is provided the use of AZD2171 or a pharmaceutically acceptable salt thereof and gemcitabine in the
manufacture of a medicament for use in the production of an anti-cancer effect in a
warm-blooded animal such as a human which is being treated with ionising radiation
30 wherein the cancer is pancreatic cancer.

According to a further aspect of the present invention there is provided the use of AZD2171 or a pharmaceutically acceptable salt thereof and gemcitabine in the

manufacture of a medicament for use in the production of an anti-tumour effect in a warm-blooded animal such as a human which is being treated with ionising radiation wherein the tumour is a non-small cell tumour of the lung.

According to a further aspect of the present invention there is provided the use of
5 AZD2171 or a pharmaceutically acceptable salt thereof and gemcitabine in the manufacture of a medicament for use in the production of an anti-cancer effect in a warm-blooded animal such as a human which is being treated with ionising radiation wherein the cancer is breast cancer.

According to a further aspect of the present invention there is provided the use of
10 AZD2171 or a pharmaceutically acceptable salt thereof and gemcitabine in the manufacture of a medicament for use in the production of an anti-tumour effect in a warm-blooded animal such as a human which is being treated with ionising radiation wherein the tumour is a tumour of the breast.

According to a further aspect of the present invention there is provided the use of
15 AZD2171 or a pharmaceutically acceptable salt thereof and gemcitabine in the manufacture of a medicament for use in the production of an anti-cancer effect in a warm-blooded animal such as a human which is being treated with ionising radiation wherein the cancer is bladder cancer.

According to a further aspect of the present invention there is provided the use of
20 AZD2171 or a pharmaceutically acceptable salt thereof and gemcitabine in the manufacture of a medicament for use in the production of an anti-tumour effect in a warm-blooded animal such as a human which is being treated with ionising radiation wherein the tumour is a tumour of the bladder.

According to a further aspect of the present invention there is provided a
25 therapeutic combination treatment comprising the administration of an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable excipient or carrier, and the administration of an effective amount of gemcitabine, optionally together with a pharmaceutically acceptable excipient or carrier and the administration of an effective amount of ionising radiation, to a warm-
30 blooded animal such as a human in need of such therapeutic treatment wherein the AZD2171, gemcitabine and ionising radiation may be administered simultaneously, sequentially or separately and in any order.

A warm-blooded animal such as a human which is being treated with ionising radiation means a warm-blooded animal such as a human which is treated with ionising radiation before, after or at the same time as the administration of a medicament or combination treatment comprising AZD2171 and gemcitabine. For example said ionising radiation may be given to said warm-blooded animal such as a human within the period of a week before to a week after the administration of a medicament or combination treatment comprising AZD2171 and gemcitabine. This means that AZD2171, gemcitabine and ionising radiation may be administered separately or sequentially in any order, or may be administered simultaneously. The warm-blooded animal may experience the effect of each of AZD2171, gemcitabine and radiation simultaneously.

According to one aspect of the present invention the ionising radiation is administered before one of AZD2171 and gemcitabine or after one of AZD2171 and gemcitabine.

According to one aspect of the present invention the ionising radiation is administered before both AZD2171 and gemcitabine or after both AZD2171 and gemcitabine.

According to one aspect of the present invention AZD2171 is administered to a warm-blooded animal after the animal has been treated with ionising radiation.

According to another aspect of the present invention the effect of a method of treatment of the present invention is expected to be at least equivalent to the addition of the effects of each of the components of said treatment used alone, that is, of each of AZD2171 and gemcitabine used alone or of each of AZD2171, gemcitabine and ionising radiation used alone.

According to another aspect of the present invention the effect of a method of treatment of the present invention is expected to be greater than the addition of the effects of each of the components of said treatment used alone, that is, of each of AZD2171 and gemcitabine used alone or of each of AZD2171, gemcitabine and ionising radiation used alone.

According to another aspect of the present invention the effect of a method of treatment of the present invention is expected to be a synergistic effect.

According to the present invention a combination treatment is defined as affording a synergistic effect if the effect is therapeutically superior, as measured by, for example,

the extent of the response, the response rate, the time to disease progression or the survival period, to that achievable on dosing one or other of the components of the combination treatment at its conventional dose. For example, the effect of the combination treatment is synergistic if the effect is therapeutically superior to the effect achievable with AZD2171 or gemcitabine or ionising radiation alone. Further, the effect of the combination treatment is synergistic if a beneficial effect is obtained in a group of patients that does not respond (or responds poorly) to AZD2171 or gemcitabine or ionising radiation alone. In addition, the effect of the combination treatment is defined as affording a synergistic effect if one of the components is dosed at its conventional dose and the other component(s) is/are dosed at a reduced dose and the therapeutic effect, as measured by, for example, the extent of the response, the response rate, the time to disease progression or the survival period, is equivalent to that achievable on dosing conventional amounts of the components of the combination treatment. In particular, synergy is deemed to be present if the conventional dose of AZD2171 or gemcitabine or ionising radiation may be reduced without detriment to one or more of the extent of the response, the response rate, the time to disease progression and survival data, in particular without detriment to the duration of the response, but with fewer and/or less troublesome side-effects than those that occur when conventional doses of each component are used.

As stated above the combination treatments of the present invention as defined herein are of interest for their antiangiogenic and/or vascular permeability effects. Angiogenesis and/or an increase in vascular permeability is present in a wide range of disease states including cancer (including leukaemia, multiple myeloma and lymphoma), diabetes, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, arterial restenosis, autoimmune diseases, acute inflammation, lymphoedema, endometriosis, dysfunctional uterine bleeding and ocular diseases with retinal vessel proliferation including age-related macular degeneration. Combination treatments of the present invention are expected to be particularly useful in the prophylaxis and treatment of diseases such as cancer and Kaposi's sarcoma. In particular such combination treatments of the invention are expected to slow advantageously the growth of primary and recurrent solid tumours of, for example, the colon, pancreas, brain, bladder, breast, prostate, lungs and skin. Combination treatments of the present invention are expected to slow advantageously the growth of tumours in

pancreatic cancer, bladder cancer, breast cancer and lung cancer, including mesothelioma and non-small cell lung cancer (NSCLC). Combination treatments of the present invention are also expected to slow advantageously the growth of tumours such as tumours of the kidney, ovary, connective tissues (eg soft tissue sarcoma) or haematopoietic system (eg lymphoma). More particularly such combination treatments of the invention are expected to inhibit any form of cancer associated with VEGF including leukaemia, multiple myeloma and lymphoma and also, for example, to inhibit the growth of those primary and recurrent solid tumours which are associated with VEGF, especially those tumours which are significantly dependent on VEGF for their growth and spread, including for example, certain tumours of the colon (including rectum), pancreas, brain, bladder, breast, prostate, lung, vulva, skin and particularly pancreatic cancer and NSCLC. More especially combination treatments of the present invention are expected to slow advantageously the growth of tumours of the pancreas. More especially combination treatments of the present invention are expected to slow advantageously the growth of tumours in non-small cell lung cancer (NSCLC). More especially combination treatments of the present invention are expected to slow advantageously the growth of tumours of the bladder. More especially combination treatments of the present invention are expected to slow advantageously the growth of tumours of the breast. More especially combination treatments of the present invention are expected to slow advantageously the growth of soft tissue sarcomas. More especially combination treatments of the present invention are expected to slow advantageously the growth of tumours of the ovary. More especially combination treatments of the present invention are expected to slow advantageously the growth of tumours of the kidney. More especially combination treatments of the present invention are expected to slow advantageously the growth of lymphomas.

In another aspect of the present invention AZD2171 and gemcitabine, optionally with ionising radiation, are expected to inhibit the growth of those primary and recurrent solid tumours which are associated with VEGF especially those tumours which are significantly dependent on VEGF for their growth and spread.

The compositions described herein may be in a form suitable for oral administration, for example as a tablet or capsule, for nasal administration or administration by inhalation, for example as a powder or solution, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) for example

as a sterile solution, suspension or emulsion, for topical administration for example as an ointment or cream, for rectal administration for example as a suppository or the route of administration may be by direct injection into the tumour or by regional delivery or by local delivery. In other embodiments of the present invention the AZD2171 of the
5 combination treatment may be delivered endoscopically, intratracheally, intralesionally, percutaneously, intravenously, subcutaneously, intraperitoneally or intratumourally. Preferably AZD2171 is administered orally. In general the compositions described herein may be prepared in a conventional manner using conventional excipients. The compositions of the present invention are advantageously presented in unit dosage form.

10 AZD2171 will normally be administered to a warm-blooded animal at a unit dose within the range 1-50mg per square metre body area of the animal, for example approximately 0.03-1.5 mg/kg in a human. A unit dose in the range, for example, 0.01-1.5mg/kg, preferably 0.03-0.5mg/kg is envisaged and this is normally a therapeutically-effective dose. A unit dosage form such as a tablet or capsule will usually
15 contain, for example 1-50mg of active ingredient. Preferably a daily dose in the range of 0.03-0.5mg/kg is employed.

Gemcitabine may be administered according to known clinical practice. For example in NSCLC the recommended dose of gemcitabine is 1000mg/m² given by 30 minute intravenous infusion. This may be repeated once weekly for three weeks, followed
20 by a one week rest period. This four week cycle may then be repeated. Dosage reduction may be necessary if the patient experiences undue toxicity. In pancreatic cancer the recommended dose of gemcitabine is 1000mg/m² given by 30 minute intravenous infusion. This may be repeated once weekly for seven weeks followed by a week of rest. Subsequent cycles may consist of injections once weekly for three consecutive weeks out
25 of every four weeks. Dosage reduction may be necessary if the patient experiences undue toxicity. In breast cancer gemcitabine (GemzarTM) may be administered intravenously at a dose of 1250 mg/m² over 30 minutes on Days 1 and 8 of each 21-day cycle. If given as well, paclitaxel may be administered at 175 mg/m² on Day 1 as a 3-hour intravenous infusion before administration of gemcitabine.

30 The dosages and schedules may vary according to the particular disease state and the overall condition of the patient. Dosages and schedules may also vary if, in addition to a combination treatment of the present invention, one or more additional chemotherapeutic

agents is/are used. Scheduling can be determined by the practitioner who is treating any particular patient.

Radiotherapy may be administered according to the known practices in clinical radiotherapy. The dosages of ionising radiation will be those known for use in clinical radiotherapy. The radiation therapy used will include for example the use of γ -rays, X-rays, and/or the directed delivery of radiation from radioisotopes. Other forms of DNA damaging factors are also included in the present invention such as microwaves and UV-irradiation. For example X-rays may be dosed in daily doses of 1.8-2.0Gy, 5 days a week for 5-6 weeks. Normally a total fractionated dose will lie in the range 45-60Gy. Single larger doses, for example 5-10Gy may be administered as part of a course of radiotherapy. Single doses may be administered intraoperatively. Hyperfractionated radiotherapy may be used whereby small doses of X-rays are administered regularly over a period of time, for example 0.1Gy per hour over a number of days. Dosage ranges for radioisotopes vary widely, and depend on the half-life of the isotope, the strength and type of radiation emitted, and on the uptake by cells.

The size of the dose of each therapy which is required for the therapeutic or prophylactic treatment of a particular disease state will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient. For example, it may be necessary or desirable to reduce the above-mentioned doses of the components of the combination treatments in order to reduce toxicity.

The present invention relates to combinations of gemcitabine with AZD2171 or with a salt of AZD2171.

Salts of AZD2171 for use in pharmaceutical compositions will be pharmaceutically acceptable salts, but other salts may be useful in the production of AZD2171 and its pharmaceutically acceptable salts. Pharmaceutically acceptable salts may, for example, include acid addition salts. Such acid addition salts include for example salts with inorganic or organic acids affording pharmaceutically acceptable anions such as with hydrogen halides or with sulphuric or phosphoric acid, or with trifluoroacetic, citric or maleic acid. In addition pharmaceutically acceptable salts may be formed with an inorganic or organic base which affords a pharmaceutically acceptable cation. Such salts

with inorganic or organic bases include for example an alkali metal salt, such as a sodium or potassium salt and an alkaline earth metal salt such as a calcium or magnesium salt. A preferred salt is AZD2171 maleate.

AZD2171 may be synthesised according to the processes described in WO 00/47212, in particular those described in Example 240 of WO 00/47212.

AZD2171 maleate salt may be synthesised according to the processes described in WO 05/061488.

Gemcitabine is commercially available.

The following tests may be used to demonstrate the activity of AZD2171 in combination with gemcitabine.

Human Calu-6 lung tumour xenografts in *Nude* mice

10^6 Calu-6 human tumour cells in 50% matrigel were injected subcutaneously (s.c.) into the flanks of athymic (*nu/nu* genotype, Swiss) mice. When tumours reached a volume of 100 to 200 mm³ (10 days after the graft), mice were randomized into groups (8 per group) and treatment started.

- The control group (Group 1) received a daily oral (p.o.) administration of AZD2171 vehicle for 25 consecutive days (day 0 – 24).
- For Group 2, the treatment consisted of a daily p.o. administration of AZD2171 alone at 3 mg/kg/administration for 25 consecutive days (day 0 – 24). AZD2171 was prepared as a suspension in 1% polysorbate 80 (i.e. a 1% (v/v) solution of polyoxyethylene (20) sorbitan mono-oleate in deionised water).
- For Group 3, the treatment consisted of a daily p.o. administration of AZD2171 alone at 1.5mg/kg/administration for 25 consecutive days (day 0 – 24). AZD2171 was prepared as a suspension in 1% polysorbate 80 (i.e. a 1% (v/v) solution of polyoxyethylene (20) sorbitan mono-oleate in deionised water).
- Group 4 received intraperitoneal (i.p.) injections of gemcitabine at 75mg/kg/injection, twice weekly on days 0, 3, 7, 10, 14, 17 and 21.
- Group 5 received daily p.o. administration of AZD2171 at 3mg/kg/administration for 25 consecutive days (day 0 – 24) combined with i.p. injections of gemcitabine at 75mg/kg/injection, twice weekly on days 0, 3, 7, 10, 14, 17 and 21.

- Group 6 received daily p.o. administration of AZD2171 at 1.5mg/kg/administration for 25 consecutive days (day 0 – 24) combined with i.p. injections of gemcitabine at 75mg/kg/injection, twice weekly on days 0, 3, 7, 10, 14, 17 and 21.

The administration volume of AZD2171 was 10.0 ml/kg (200 µl for a 20 g mouse). The

- 5 injection volume of gemcitabine was 10.0 ml/kg (200 µl for a 20 g mouse).

Group	Treatments	Combined drug doses (mg base/kg/inj.)	Adm. route	No. Treatments	No. Treatment /day	Days-interval between treatment (Days)
1	Vehicle of AZD2171	0.0	p.o.	25 p.o.	1 p.o.	1
2	AZD2171	3	p.o.	25 p.o.	1 p.o.	1
3	AZD2171	1.5	p.o.	25 p.o.	1 p.o.	1
4	Gemcitabine	75	i.p.	7 i.p.	1 i.p.	3-4
5	AZD2171 + Gemcitabine	3 for AZD2171 75 for Gemcitabine	p.o. for AZD2171 i.p. for Gemcitabine	25 p.o. 7 i.p.	1 p.o. 1 i.v.	1 for p.o. 3-4 for i.p.
6	AZD2171 + Gemcitabine	1.5 for AZD2171 75 for Gemcitabine	p.o. for AZD2171 i.p. for Gemcitabine	25 p.o. 7 i.p.	1 p.o. 1 i.v.	1 for p.o. 3-4 for i.p.

- Tumour volumes (mm³) were assessed at least twice weekly by bilateral Vernier caliper measurement and, taking length to be the longest diameter across the tumour and width the corresponding perpendicular, calculated using the formula $(\pi/6) \times (\text{length} \times \text{width}) \times \text{the square root of } (\text{length} \times \text{width})$. Growth inhibition from the start of treatment was assessed by comparison of the differences in tumour volume between control and treated groups. Additionally, the effects of combination treatment are assessed by comparing tumour growth in the group of animals receiving gemcitabine plus AZD2171 with the tumour growth in the groups where animals received single agent therapy alone.

The data for combination studies for AZD2171 and gemcitabine, wherein AZD2171 was dosed at 3 or 1.5mg/kg are shown in Figures 1 and 2.

The combination of gemcitabine with AZD2171 dosed at 3mg/kg produced a significantly greater inhibition of tumour growth than gemcitabine alone or AZD2171 alone (Figure 1). The inhibition of tumour growth produced by the combination of the two agents AZD2171 and gemcitabine was still significantly greater than that produced by either agent alone

5 when the dose of AZD2171 was reduced to 1.5mg/kg (Figure 2).

CLAIMS

1. Use of AZD2171 or a pharmaceutically acceptable salt thereof and gemcitabine in the manufacture of a medicament for use in the production of an antiangiogenic and/or
5 vascular permeability reducing effect in a warm-blooded animal such as a human.

2. Use of AZD2171 or a pharmaceutically acceptable salt thereof and gemcitabine in the manufacture of a medicament for use in the production of an anti-cancer effect in a warm-blooded animal such as a human.

3. Use of AZD2171 or a pharmaceutically acceptable salt thereof and gemcitabine in the manufacture of a medicament for use in the production of an anti-tumour effect in a warm-blooded animal such as a human.

4. Use of AZD2171 or a pharmaceutically acceptable salt thereof and gemcitabine in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human which is being treated with ionising radiation.

5. Use of AZD2171 or a pharmaceutically acceptable salt thereof and gemcitabine in the manufacture of a medicament for use in the production of an anti-cancer effect in a warm-blooded animal such as a human which is being treated with ionising radiation.

6. Use of AZD2171 or a pharmaceutically acceptable salt thereof and gemcitabine in the manufacture of a medicament for use in the production of an anti-tumour effect in a warm-blooded animal such as a human which is being treated with ionising radiation.

7. Use according to claim 3 or claim 6 wherein the tumour is a tumour of the pancreas, bladder or breast or is a non-small cell tumour of the lung.

8. Use according to claim 2 or claim 5 wherein the cancer is non-small cell lung cancer (NSCLC), bladder cancer, breast cancer or pancreatic cancer.

9. A pharmaceutical composition which comprises AZD2171 or a pharmaceutically acceptable salt thereof, and gemcitabine in association with a pharmaceutically acceptable excipient or carrier.

5 10. A kit comprising AZD2171 or a pharmaceutically acceptable salt thereof and gemcitabine.

11. A method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human, which comprises
10 administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of gemcitabine.

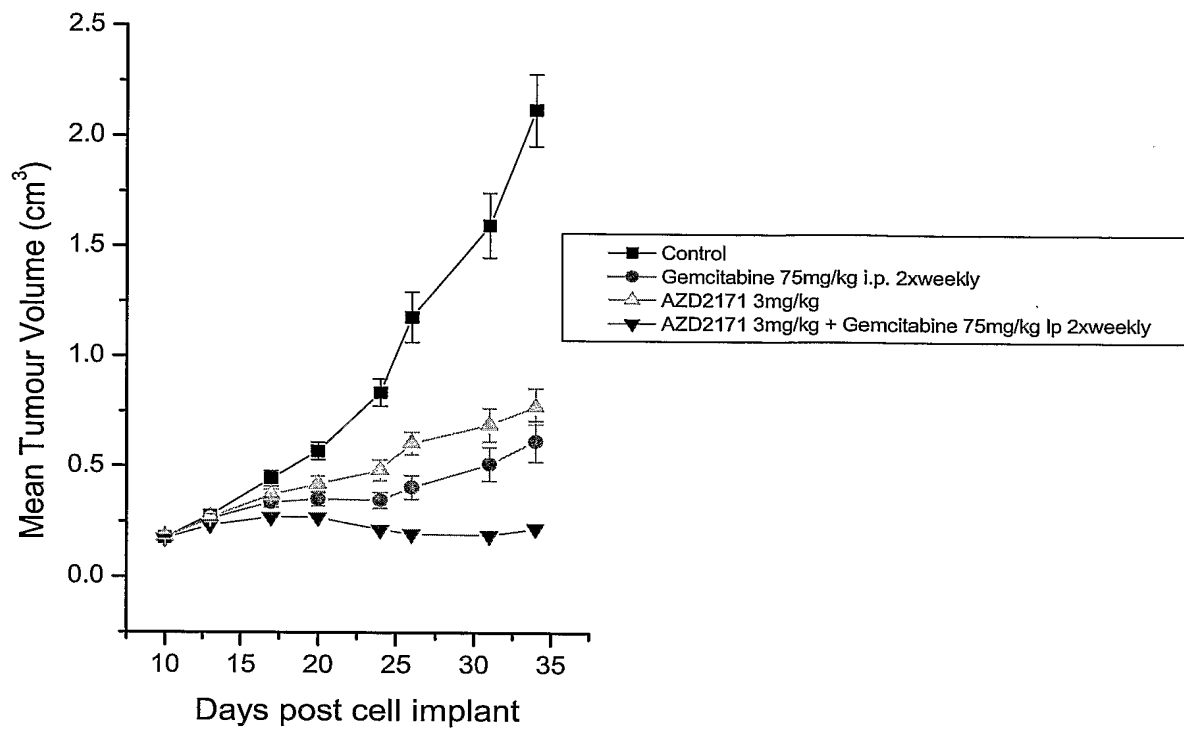
12. A method for the production of an antiangiogenic and/or vascular permeability
15 reducing effect in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of gemcitabine and before, after or simultaneously with an effective amount of ionising radiation.

20

13. Use according to claim 3 or claim 6 wherein the tumour is a tumour of the kidney, ovary, connective tissues or haematopoietic system.

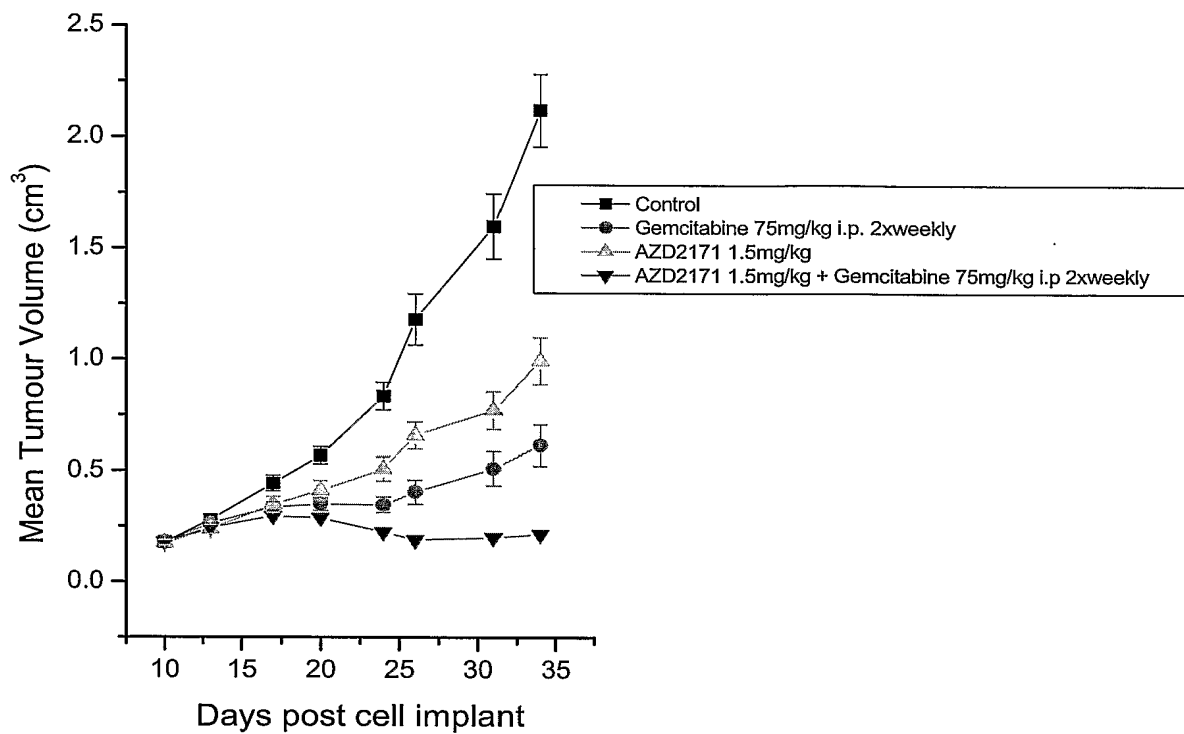
14. Use according to claim 2 or claim 5 wherein the cancer is lymphoma, renal cell
25 carcinoma, ovarian cancer or soft tissue sarcoma.

- 1/2

Figure 1

AZD2171 3mg/kg vs AZD2171 3mg/kg + Gemcitabine 75mg/kg $p < 0.001$

5 Gemcitabine 75mg/kg vs AZD2171 3mg/kg + Gemcitabine 75mg/kg $p < 0.001$

$-2\frac{1}{2}$ **Figure 2**

5 AZD2171 1.5mg/kg vs AZD2171 1.5mg/kg + Gemcitabine 75mg/kg $p < 0.001$

Gemcitabine 75mg/kg vs AZD2171 1.5mg/kg + Gemcitabine 75mg/kg $p < 0.001$